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Early life factors initiate a 'vicious circle' of affective and gastrointestinal symptoms: A longitudinal study

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Abstract

Objective: Functional gastrointestinal disorders (FGID) have been shown to be associated with both comorbid mood disorders and traumatic events such as abuse earlier in life. In a longitudinal study, we tested a model that hypothesized: (i) childhood abuse was associated with subsequent mood disorder and pain or interference in life by bowel symptoms both directly and indirectly via neurotic personality; and (ii) an ongoing cycle of mood disorder impacts on bowel symptoms.

Design: Subjects from the general population classified as irritable bowel syndrome and/or functional dyspepsia (IBS/FD, $n = 207$) or free of FGID ($n = 100$) were prospectively studied every 6 months over 18 months. In addition to bowel symptom interference and abdominal pain, measures of personality (neuroticism), childhood abuse history, depression, and anxiety were obtained. The hypothesized model was tested via Path Modelling.

Results: Childhood abuse was found to be directly associated with neuroticism but only indirectly associated with baseline interference and mood disorders (via neuroticism). The data further supported an ongoing cycle of elevations in mood disorders and pain/interference by bowel symptoms. The data supported direct effects of interference at one time point on interference at the subsequent time point in addition to indirect effects of prior anxiety and depression. Repeating the model with pain frequency as the outcome yielded almost identical findings which suggests the findings are generalized across domains of symptoms and quality-of-life.

Conclusion: Our data provide support for a model characterized by a 'vicious circle' between mood disorders and FGID symptoms in adulthood, with initial input from early life factors.

Keywords

Anxiety and depression, biopsychosocial, childhood abuse, functional dyspepsia, irritable bowel syndrome

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Introduction

The functional gastrointestinal disorders (FGIDs) as a group are common conditions with overall FGID prevalence estimated at approximately one-third of the population.[1] The 'prototypical' upper FGID is functional dyspepsia (FD) while a well-studied lower FGID is the irritable bowel syndrome (IBS). Both IBS and FD can be debilitating conditions that are associated with a significant reduction in quality of life[2,3] and major economic impact.[4–6] Being functional conditions, they are not associated with any identifiable pathology and neither their aetiology nor maintenance are well understood.

Some insights into the aetiopathogenesis of IBS come from data showing an association with past adverse experiences, particularly sexual and physical abuse during childhood,[7,8] although these findings have not always been replicated.[9] IBS has also been shown to be associated with higher scores on the neuroticism domain of personality.[10] Since personality is generally thought to be a stable (trait) characteristic[11] largely under genetic control,[12] it may also be a feature

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developed early in life that predisposes individuals to develop IBS or other FGIDs.

FGIDs have a well-documented overlap with mood disorders, particularly elevated anxiety and depression, in cross-sectional studies.[13,14] While these cross-sectional studies demonstrate important associations between FGIDs and mood disorders, they do not allow any conclusions on causal or temporal relationships between these variables. One longitudinal follow-up study, using questionnaires sent with a 12-year interval to a random population sample, showed evidence of a bi-directional interaction between FGID symptoms on one hand and anxiety and depression on the other hand.[15]

To date, prospective follow-up studies on short-term interactions between mood disorders and FGID in carefully characterized patient samples are lacking. The present study aims to test the hypothesis that early life factors (abuse and neuroticism) predispose to elevated anxiety and depression, which subsequently interact in a cyclical fashion over time with gastrointestinal symptoms, particularly abdominal pain, and its interference with daily life. While IBS and FD are characterized by a number of features, chief among these, from a patient perspective, are pain and interference with daily activities.[16,17]

If the hypothesized model is supported by data, it would lead to a better understanding of the aetiopathogenesis of FGID and suggest that early life interventions might prevent its occurrence in some individuals and that treatments aimed at comorbid anxiety and depression may break the 'vicious circle' and, hence, reduce FGID symptoms.

Methods

Subjects

FGID subjects were recruited from the cohorts of two previously published studies[1,18] that all represented random samples from the community. After in-depth interviews, among those who agreed to participate, using the Structured Interview on Bowel Symptoms (SIBS), we identified 207 subjects who met the Rome I criteria for IBS and/or FD. The Rome I criteria were the current standard at the time that these data were collected in 1999–2001.

Controls consisted of people from studies[1,18] who did not report having abdominal pain for more than 1 month. There were no significant differences between those who agreed to participate in the current study ($n = 100$) and those who had refused in terms of age, sex, educational level attained, and country of birth, except that controls from study II were slightly albeit significantly older (mean ± SD age 53.4 ± 15.9 years) than those who refused (46.9 ± 14.7 years). The sampling frame for these surveys consisted of the 1996 electoral roll for the local government areas of Penrith and the Blue Mountains which are relatively homogeneous in terms of their sociodemographics and ethnic composition with the Australian population.[19]

The sample available at the baseline timepoint for this research was therefore 207 IBS/FD and 100 controls for a total sample of 307 subjects.

Measures

Symptom status. This Structured Interview for Bowel Symptoms (SIBS) was developed at the Nepean Hospital to ensure that a reliable diagnosis of IBS or functional dyspepsia can be made according to the Rome I criteria. The SIBS was directly based on the validated Rome criteria[8] and in large part on the previously validated Bowel Symptom Questionnaire.[20]

The SIBS also provides a measure of the interference of symptoms on life and activities. Two measures were used as outcomes in this study: (i) the number of days in the previous 4 weeks that the respondent had experienced pain in their stomach or abdomen ('pain'); (ii) how much that pain interfered with life and activities ('interference') on a scale of 'not at all' to 'extremely'.

Self reported abuse

Childhood (13 years or younger) sexual and non-sexual (physical and verbal) abuse was assessed via valid self-report.[7,21] A person was defined as having been sexually abused in this study if they had a positive response to any of the following sexual abuse items, according to the method of Leserman et al.:[21] that an adult or caregiver had threatened to have sex with them, touched the sex organs of their body, made them touch the sex organs of someone else, tried forcefully to have sex, or succeeded in having sex with them. Physical abuse was defined as any of the following incidents by an adult or caregiver occurring at least occasionally: life seriously threatened and/or hit, kicked, or beaten. Emotional/verbal abuse was defined as any of the following incidents by an adult or caregiver occurring at least occasionally: verbally abused, severely criticized or insulted and/or bullied, threatened, or deliberately humiliated. Abuse questions were asked on a 4-point scale of never, seldom, occasionally, or often. A person was considered to have suffered from physical abuse or emotional abuse if that abuse occurred at least on an occasional basis. Based on previous studies showing an increased prevalence of all these three types of abuse in FGID,[22,23] no distinction was made between these three different types in the present study (i.e. absence or

presence of any type of abuse was used as a dichotomous variable in our a priori hypothesized model).

Neuroticism. The validated self-report scale Eysenck Personality Questionnaire-Revised[24] was used to assess the personality trait of neuroticism in the current study. Individuals who score high on the neuroticism scale tend to be worriers. They also tend to have strong emotional reactions to all sorts of stimuli and take a lot longer to calm down following arousal.[25]

Anxiety and depression. Composite International Diagnostic Interview-auto (CIDI) administrator version[26] is a valid[27] computerized structured interview used to assess psychiatric illness. Lifetime and current standard psychiatric diagnostic criteria including International Classification of Disease-10 and Diagnostic and Statistical Manual of Mental Disorder-IV diagnosis for anxiety, depression, and somatization were generated for this study. A diagnosis of anxiety included diagnoses for panic disorder, agoraphobia, social phobia, and generalized anxiety disorder. Depression included major depressive disorder and dysthymic disorder.

Procedure

The study followed a naturalistic, longitudinal design in which individuals were identified as IBS/FD or control at baseline and was approved by the Wentworth Area Health Service Ethics committee. Individuals were initially sent a letter outlining the nature of the study and were followed up with a telephone call 1 week later to obtain preliminary consent and to arrange a time for them to come to the Nepean Hospital for an interview. At this interview, subjects gave formal written consent and were interviewed by an independent researcher on their symptom status using the SIBS, which took approximately 20 min. A second interviewer, who was blinded to the symptom information, administered the CIDI. Subjects then completed the series of validated self-report questionnaires, which took up to 1 hour to complete. Subjects were then followed up with an interview and self report measures identical to the first interview every 6 months for a period of 18 months, with the exception that the CIDI was only administered at the initial and the 1-year follow up. A summary of the measures used at each time point in the models is summarized in Table 1.

Table 1. Measures used at each time point in models

Measure	Baseline	6 months	12 months	18 months
Abuse	+	+	+	+
Neuroticism	+	+	+	+
Anxiety	+	−	+	−
Depression	+	−	+	−
Interference	+	+	+	+
Pain	+	+	+	+

Statistical methods

Descriptive statistics for the sample have been reported as mean and standard deviation for numeric measures and as percentage and sample size for categorical variables.

The primary outcome hypothesized in this study is interference with life and activities (5-point scale) and the model incorporating this outcome is considered the primary analysis. Pain frequency (days per 4 weeks) has also been included as alternate outcome to enable comment on the generalizability of the model. While pain may be theorized to be a precursor to interference, at baseline these two measures correlated at Pearson's $r = 0.51$, indicating they share only approximately 25% variance and therefore it can be argued they represent related but distinct aspects of symptoms and quality-of-life.

Path modelling[28] has been used to test an a priori hypothesized model representing the sequential interactions between mood and pain/interference. The focus in this paper is on understanding pathways which are potentially causal. Given the requirement for correct temporal order, concurrent pathways are not informative and, hence, not all mathematically possible paths were included in the analysis despite being demonstrated in previous studies.[29] The hypothesized paths have been reported empirically via pairwise Pearson correlation coefficients to describe the paths as observed (i.e. ignoring other elements of the model). The model itself has been implemented as a path model for both interference and pain in which interest lies in the direction and statistical significance of the individual path coefficients (controlling for all other paths in the model) as well as the overall fit of the model to the data. The standardized path coefficients reported are equivalent to standardized regression coefficients fitted in a series of simultaneous regression models.

The logic of this model is that early life factors (abuse and neuroticism) predispose individuals towards elevated anxiety and depression and then in a cyclical fashion, increased mood disturbance is followed by bowel symptoms, particularly abdominal pain, and its interference with daily life. The model posits that early life factors influence initial mood levels, but since subjects are studied at an arbitrary time of life, there may

already have been some effect on interference and pain. Initial mood and interference/pain levels are hypothesized to influence subsequent mood level which in turn influences later interference and pain levels. For the model to be supported, all hypothesized associations must be positive.

The hypothesis tests employed assume the variables included follow a multivariate normal distribution. Examination of the individual variable distributions reveals that substantial non-normality and univariate normality is a necessary condition for multivariate normality. For this reason, we have employed the nonparametric bootstrap to estimate parameter standard errors and hence *p*-values. In some cases, *p*-values obtained from bootstrap analysis are larger than those from the naïve analysis and both have been reported. While bootstrap estimation may increase the size of the standard error and hence *p*-value, it has no effect on the estimated effect size (path coefficient). The model was fitted using MPlus version 5 software in which anxiety and depression were nominated as categorical (binary) variables and hence analysis for paths leading to these variables are based on binary logit models. The overall model fit represents how well the hypothesized model reproduces the observed variance-covariance structure in the data. There is no single optimal measure of goodness-of-fit for path models and hence a combination of statistics is reported. A statistic that follows a Chi-squared distribution under the null hypothesis yields a statistically non-significant result when the model fits adequately, but it can be overly sensitive when sample size is large.[30] Another rule-of-thumb is that the ratio of the statistic to degrees of freedom <2.0 indicates adequate fit.[30] Additionally, the Tucker–Lewis index (TLI) and the comparative fit index (CFI) are reported. When the model fits the observed variance-covariance structure well, both the TLI and CFI are close to 1.0 with values >0.95 generally considered to be adequate.[30] Statistical power was assessed for the final outcome variable in each model using the method described in Blanchard et al.[29] The power for multiple regression when the model-explained variance was 10% was >0.95 at the 0.05 level of statistical significance (two-tailed).

Results

Subjects

The sample consisted of 207 individuals diagnosed with IBS ($n=156$) or FD ($n=51$) according to Rome I criteria[31] and $n=100$ healthy volunteers. IBS and FD were combined in this study as there is evidence that there is considerable overlap between these two disorders.[32,33] Moreover, others have shown that IBS and FD share a similar demographic[34] and psychological profile[34,35] and some of the underlying mechanisms of IBS and FD may also be similar.[36] By sampling design, the sample was overall 70% female and this was similar in both IBS/FD (69%) and control groups (71%, $p=0.7$). IBS/FD subjects were on average slightly younger (mean ± SD 46.4 ± 13.7 years) than control subjects (53.2 ± 15.5 years; $p<0.0005$).

Overall, 31% of subjects suffered from clinically elevated anxiety at baseline and 33% had elevated depression scores. Mood disturbance was increased in IBS/FD vs. controls, with elevated anxiety in 14% of controls compared with 40% of IBS/FD ($p<0.0001$) and elevated depression scores in 18% of controls compared with 40% of IBS/FD ($p=0.0002$). Neuroticism scores were also higher in IBS/FD (5.6 ± 3.2) than controls (4.1 ± 3.2; $p=0.0002$). Childhood abuse was reported by 50% of the sample and rates were similar in IBS/FD and control groups ($p=0.2$).

Interference with daily life was a relatively severe outcome and at baseline was less frequent with mean 1.8 days/4 weeks (median ± SD 1 ± 1.2, maximum 5) than the occurrence of pain with a mean of 5.9 days/4 weeks (2 ± 8.4, maximum 28).

Response/dropout rates

Although the pattern of missing data varies across measures, the number of individuals contributing measurements at baseline, 6 months, 12 months, and 18 months were 307, 261, 247, and 229, respectively, yielding response rates from 85% overall (83% in IBS/FD, 90% in controls) at 6 months to 75% overall (74% in IBS/FD, 76% in controls) at 18 months.

Observed associations

As shown in Figure 1, childhood abuse was positively associated with both elevated anxiety and depression prevalence at baseline as was neuroticism. Neuroticism was positively associated with higher interference with life and activities at baseline, but childhood abuse was not. Associations between successive interference with life and activities scores were all positive, of at least moderate magnitude and statistical significance. Elevated baseline anxiety and depression as well as higher baseline interference scores were all positively and statistically significantly associated with higher interference with life and activities at 6 months. Interference with life and activities at 6 months was associated with higher anxiety and depression at 12 months although the association only reached statistical significance for anxiety. Depression at 12 months, but not anxiety, was associated with higher interference with life and activities scores at (Figure 1).

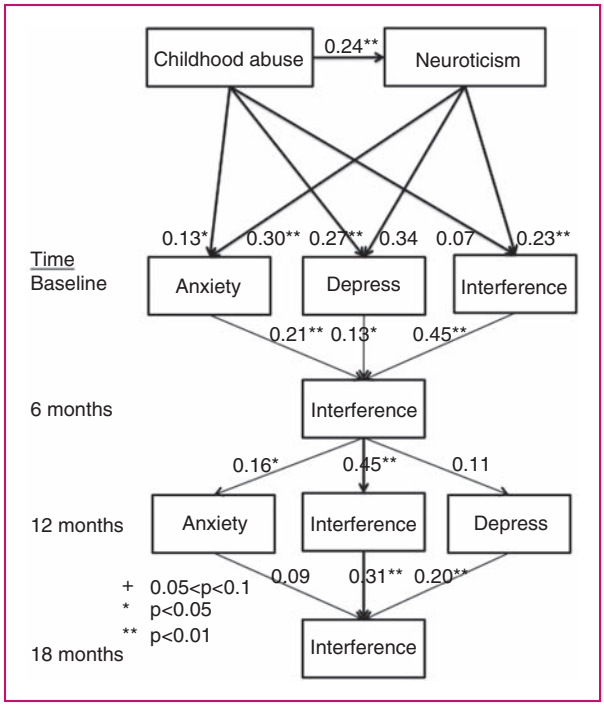

Figure 1. Observed (bivariate) associations in the interference model.
Numbers are Pearson correlation coefficients.

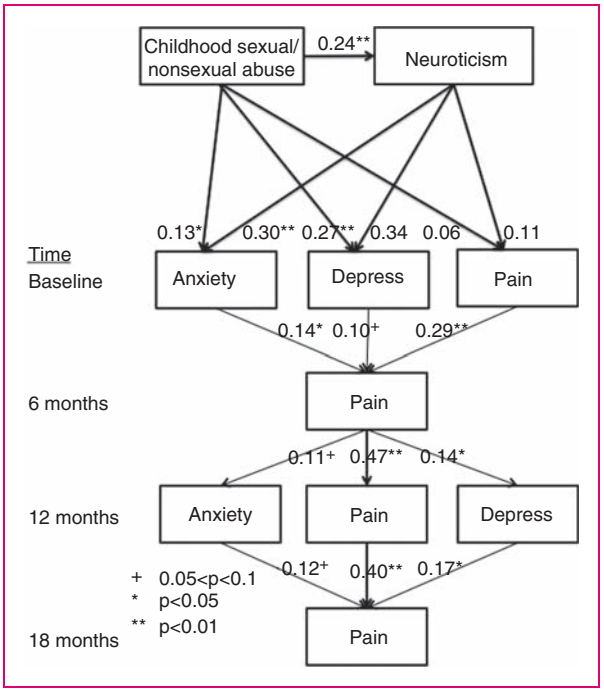

Figure 2. Observed (bivariate) associations in the pain model. Numbers are Pearson correlation coefficients.

The pattern of observed bivariate correlations between successive pain and mood scores were generally similar to those found for interference (Figure 2). The correlation between baseline anxiety and 6-month pain was slightly lower than for interference, as was the correlation between 6-month pain and 12-month anxiety.

Path model

Path analysis suggests that abuse during childhood was positively associated with elevated levels of neuroticism (Figure 3), which was strongly positively associated with baseline prevalence of anxiety and depression and moderately elevated scores on interference with life and activities but not pain. However, there was no evidence that childhood abuse was directly associated with anxiety prevalence or interference level, but it was modestly positively associated with prevalence of depression. Elevated baseline anxiety and depression as well as higher baseline interference with life and activities scores were all positively and statistically significantly associated with higher interference at 6 months (Figure 3), with all standardized path coefficients in the moderate range (0.27–0.40). Interference at 6 months was strongly associated with higher odds of anxiety and depression at 12 months (Figure 3), with standardized path coefficients 0.67 and 0.80, respectively, as well as moderately higher levels of interference with life and activities at that time (standardized path coefficient 0.40). Depression and interference level at 12 months, but not anxiety, were associated with higher interference with life and activities scores at 18 months (Figure 3).

While path coefficient directions supported the hypothesized model, the level of statistical significance depended upon whether standard errors are derived using bootstrap methods or are based on conventional inference. While the bootstrapping approach increaseed the estimated statistical uncertainty around the path coefficients, it did not alter the path coefficients themselves. Measures of overall fit indicated the model did not adequately reproduce the observed variance-covariance structure in the data. The Chi-squared test yielded $\chi^2/\mathrm{df} = 6.1$ ($p < 0.0001$) and TLI and CFI were 0.66 and 0.48, respectively, all of which indicated a poor overall fit.

The path model incorporating pain (Figure 4) indicated patterns of cyclical relationships that closely paralleled those for interference (Figure 3). Baseline anxiety, depression, and pain all positively and independently predicted pain at 6 months, which predicted anxiety and depression at 12 months (Figure 4) with mild-to-moderate standardized effect sizes (standardized path coefficients 0.18–0.29). Pain at 6 months had moderate-to-strong associations with anxiety,

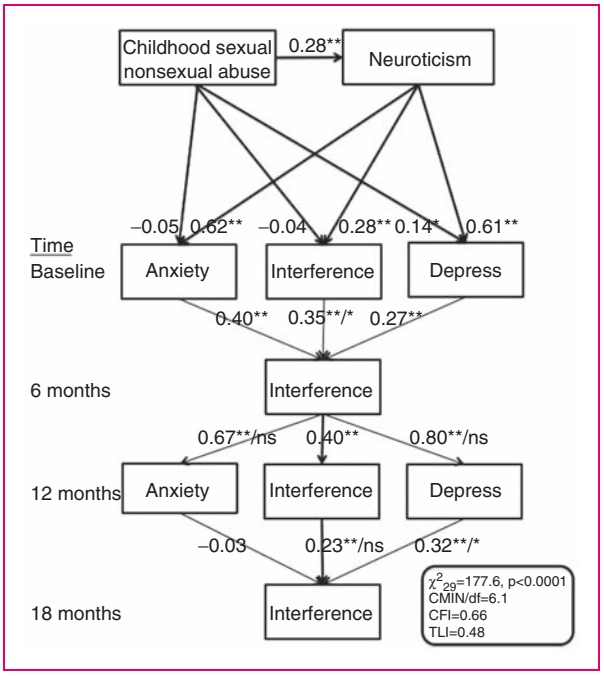

Figure 3. Path model operationalizing hypothesized model of early life influences on later biopsychosocial relationship between mood and bowel interference.
Numbers are standardized path coefficients. $*p < 0.05$; $**p < 0.01$. Where the conventional and bootstrapped p-values differed, they are reported as $p_{conventional}/p_{bootstrap}$.

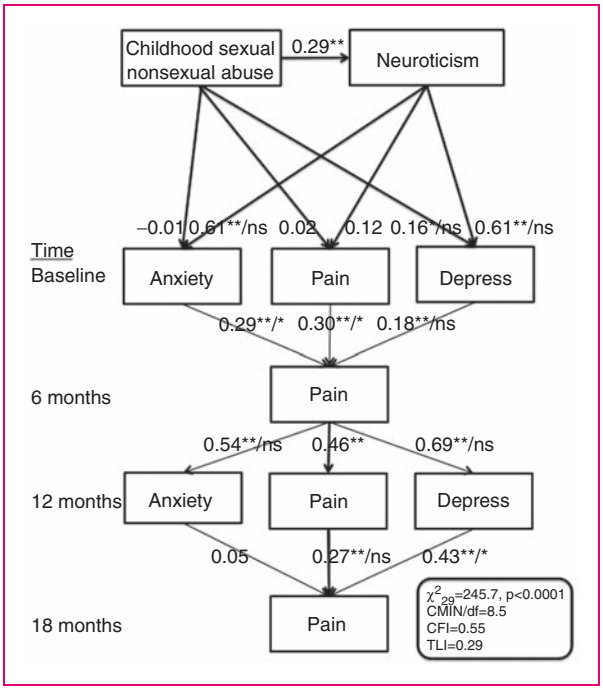

Figure 4. Path model operationalizing hypothesized model of early life influences on later biopsychosocial relationship between mood and bowel pain.
Numbers are standardized path coefficients. $*p < 0.05$; $**p < 0.01$. Where the conventional and bootstrapped p-values differed, they are reported as $p_{conventional}/p_{bootstrap}$.

depression, and pain at 12 months (standardized path coefficients 0.46 to 0.69). Depression at 12 months, but not anxiety, predicted pain at 18 months (Figure 4) with all associations in the model being positive. Notably, the path from depression at 12 months to pain at 18 months was stronger in effect size than the path from pain at 12 months to pain at 18 months. Similar to the findings for interference, the pain model also does not yield an overall adequate fit with χ^2/df 8.5 ($p < 0.0001$) and TLI and SFI 0.55 and CFI 0.29, respectively, all of which indicate a poor overall fit. As was the case with interference, the level of statistical significance depended, in some cases, on whether standard errors were derived using conventional inference or bootstrap methods. We noted, however, that whenever a path reached statistical significance using conventional methods, the effect size, expressed through the standardized path coefficient, was always at least moderate.

Discussion

Disparate cross-sectional studies have suggested connections between childhood events and subsequent adult psychological disturbance which may, via the brain–gut axis, influence the onset of a range of FGIDs,[15,37] including IBS and FD. The present study sought to test a model that postulated childhood sexual and non-sexual abuse together with neuroticism as the initial drivers of both adult mood disturbance and interference with life and activities by bowel symptoms. The model then proposes maintenance of bowel symptom interference through an ongoing interaction between mood disturbance and bowel symptoms. Rather than approximate longitudinal analyses from cross-sectional data, the present work was based on prespecified longitudinal measurements taken at four time points over an 18-month period.

The current data supported the proposed model to the extent that all paths in the model were in the direction predicted by the model, all had at least moderate effect sizes and most reached statistical significance (Figures 3 and 4). Hence, this longitudinal study supports the hypothesis that traumatic childhood events may lead to adult mood disturbance via increased neuroticism which we would argue involves a tendency to interpret events that impinge on the individual in a negative light. That outcome is then associated with higher abdominal pain ratings and higher interference with life and activities. Interestingly, the influence of childhood abuse on initial anxiety and depression levels appeared to be completely mediated via

neuroticism with effectively no direct influence. However the underlying cause of the association between childhood events and adult FGID onset cannot be answered by our data. It has been suggested that maladaptive responses to pain, including catastrophic misinterpretations, may lead to an ongoing cycle of anxiety and pain maintenance.[38] Notably, the overall model fit in the present study was not ideal, and while this does not argue against the basic principles of the model, it does suggest that there are components not included in the model that contribute to bowel symptoms ratings and interference with life and activities. This is not surprising, since the aim of this study was to test specific a priori hypotheses rather than to develop a detailed model of the genesis and maintenance of FGID from childhood to adulthood. A number of potentially confounding factors, such as the individual's social support system and access to and quality of care for GI symptoms, were not taken into account. Furthermore, taking into account the likelihood that IBS, along with other FGIDs, is a heterogeneous condition,[37] there may be no single detailed model that fits all individuals.

Our results stand in contrast to Blanchard et al.[29] who concluded that stress at one time was not directly linked with stress at a subsequent time point. Our study is not, however, directly comparable with theirs in three important respects. One is that Blanchard et al.[29] studied the effect of stress on GI symptoms over an acute period of 3 weeks in comparison with our much longer time course of 18 months. The second is that our study was not concerned with stress as such but rather psychiatrically diagnosed anxiety and depression and while these constructs are likely to be positively correlated they are also quite different. The third is that Blanchard et al.[29] assessed their data for the best-fitting model whereas our aim was to test specific and a priori specified hypotheses.

We suggest there are several key lessons from our data: (i) childhood factors (abuse in this case) appear to set up a lifetime of negative appraisal of events via elevated levels of neuroticism; (ii) elevated neuroticism is associated with higher prevalence of anxiety and depressive (mood) disorders; (iii) mood disorders predict increased reporting of abdominal pain and interference with life and activities at later time points; and (iv) abdominal pain and interference with life and activities predict increased anxiety and depression at later time points. Hence, the association between GI symptoms and mood disorders acts in a 'vicious circle' that continues over a prolonged period.

While we feel the data provide support for childhood abuse leading to long-term psychological sequelae, we also acknowledge that there are other possibilities. One is that childhood abuse results in long-term alterations in biological as well as or instead of psychological systems. Danese and McEwen[39] recently published a review suggesting that adverse childhood experiences cause long-term alterations in the nervous, endocrine, and immune systems which might provide an alternate or complementary pathway to the phenomena reported here, as these biological phenomena may be the underlying pathophysiological basis of the psychological paths we describe here. We also note that childhood abuse can be measured on multiple dimensions and so, for particular outcomes, specific forms of abuse, such as childhood sexual abuse, may be more important than others. Although the data are not shown, we did investigate alternate coding schemes for childhood abuse, including a none/moderate/severe scale, and sexual vs. non-sexual, but concluded that childhood abuse of any type best fits the data.

The strengths of the current study include the use of interview data to assess both gastrointestinal and psychological symptoms, its pre-specified longitudinal follow-up design, the small drop-out rates (15% at 6 months through to 25% at the final 18-month time point), and the use of state-of-the-art statistical techniques to model the associations between different factors over time.

The ideal study of the genesis and maintenance of FGID would involve a large birth cohort followed until well into adulthood in which a wide range of clinical and psychological measures would be taken frequently. We applied the older Rome I criteria to document FGID status but these remain the best-validated criteria.[8] The present study also suffered from both measurements being taken over a relatively short time frame and having to rely on recall of childhood abuse events. It is also possible that there are other, well-validated disease impact measures than those recorded in this work that would have been useful and could be incorporated into future work. The present design did, however, allow us to study the principles of the hypotheses that underpin the model in an unbiased fashion even if not all the detailed mechanisms. An interesting avenue of further research would be to examine whether childhood abuse in particular is relevant to later onset of FGIDs or is just one exemplar of a relevant childhood trauma and others also exist. Possible examples might include intubation of the gastrointestinal tract, infectious insults in early childhood, or perinatal under-nutrition. For example, Bengston et al.[40] evaluated 12,700 Norwegian twins born between 1967 and 1979, and showed that twins with a birthweight below 1500 g were significantly more likely to develop IBS. Anand et al.[41] showed that gastric suction at birth was associated with being discharged from the hospital with a diagnostic code for a functional intestinal disorder later in life,

whereas maternal, perinatal, and other confounding variables were not significant.

Our findings may have a number of clinical implications. While we acknowledge that IBS and FD are heterogeneous disorders and it is likely that no one treatment approach will fit all, our data suggest an important role for psychological interventions in individuals with these disorders. Indeed psychological therapy, either counselling-based or pharmacological, may be key to breaking the cycle suggested by our data. While confirmation in an interventional study is desirable, based on the current analysis, we propose that gastroenterologists consider a multidisciplinary approach to the treatment of patients with IBS or FD whose symptoms interfere with daily life as standard practice rather than as the exception.

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Conflict of interest

The authors declare that there is no conflict of interest.

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